AMENDMENTS TO THE SPECIFICATION:

Please replace the existing Sequence Listing with the substitute Sequence Listing enclosed herewith.

Please amend this application on page 1, line 1, by inserting the following new paragraph:

This application is a divisional of U.S. Patent Application No.09/763,590 filed February 26, 2001, which was filed under 35 U.S.C. 371 based on International Application PCT/JP99/04718, filed August 31, 1999, both of which are herein incorporated by reference.

Please replace the paragraph on page 5, lines 2-9, with the following paragraph:

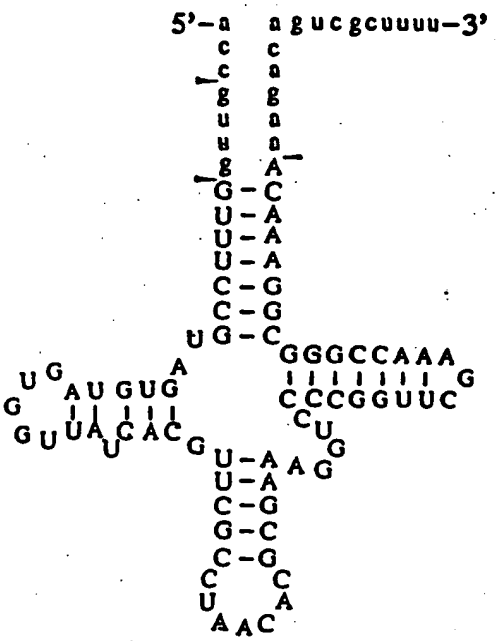
1. A ribozyme comprising a nucleotide sequence having the following base sequence (I) or (II):

base sequence (I) (SEQ ID No. 1): 5'-ACCGUUGGUUUCCGUAGUGU AGUGGUUAUCACGUUCGCCUAACACGCGAAAGGUCCCCGGUUCGAAACCGGGCAC UACAAACACAACACUGAUGAGGACCGAAAGGUCCGAAACGGGCACGUCGGAAACGG UUUU[[U]]-3'

base sequence (II)(SEQ ID NO. 2): 5'-ACCGUUGGUUUCCGUAGUGUAGUG GUUAUCACGUUCGCCUAACACGCGAAAGGUCCCCGGUUCGAAACCGGGCACUACAA ACCAACACACAACACUGAUGAGGACCGAAAGGUCCGAAACGGGCACGUCGGAAACG GUUUU[[U]]-3'.

Please replace the paragraph beginning on page 5, line 26, and continuing through the tRNA structure on page 6, line 3, with the following paragraph:

8. An RNA variant (mature $tRNA^{Val}$) adopting the following secondary structure (I), wherein said RNA variant comprises a bulge structure introduced in the region in which hydrogen bonds form between nucleotides 8 to 14 and nucleotides 73 to 79.



(I)
(SEQ ID No. 4)

Please replace the paragraph beginning on page 14, line 19 with the following paragraph:

Figure 1 (A-E) shows the secondary structures of $tRNA^{Val}$-ribozymes that were predicted by computer folding. The sequence of hammerhead ribozyme (bold capital letters) was ligated with that of $tRNA^{Val}$ sequence (capital letters) by means of various linker sequences. The sequences that correspond to the internal promoter of seven-

base-deleted $tRNA^{Val}$, namely the A and B boxes, are indicated by shaded boxes. Diagrams A to D show the secondary structures of $tRNA^{Val}$-ribozyme 1 (Rz1), 2 (Rz2), 3(Rz3) and 4(Rz4), respectively. The recognition arms of ribozymes are indicated by underlining. Diagram E shows the secondary structure of the transcript of human placental $tRNA^{Val}$. The tRNA is processed at three sites (arrowheads) to yield in the mature $tRNA^{Val}$ (capital letters).

Please replace the paragraph beginning on page 15, line 6 with the following paragraph:

Figure 2 (A and B) indicates the cleavages mediated by $tRNA^{Val}$-ribozyme *in vitro*. Panel A is a schematic representation of the substrate RNA (the substrate RNA corresponds to nucleotides 500-711 of pNL432, namely the U5 region of HIV-1 RNA). The substrate RNA was cleaved into two fragments by the $tRNA^{Val}$-ribozyme (5' fragment, 70-mer; 3' fragment 156-mer). Panel B is an autoradiogram showing the results of cleavage reactions. Lanes; M, markers; vector, $tRNA^{Val}$ vector alone without a ribozyme; Rz1 - ribozyme 1; Rz2 - ribozyme 2; and Rz3 - ribozyme 3.

Please replace the paragraph beginning on page 15, line 16 with the following paragraph:

Figure 3 (A-C) indicates the stability of $tRNA^{Val}$-ribozyme *in vivo*. Panel A is a schematic representation of pUC-Rr that allowed normalization of the efficiency of transfection by the use of a reference gene. The reference gene was expressed downstream of the ribozyme-expression cassette. The sequences of the promoter and terminator were the same, respectively, in the two expression cassettes. Panel B

shows steady-state levels of expression of $tRNA^{Val}$-ribozyme. This figure shows Northern blotting analysis with the probe specific for the ribozyme (upper) and for the reference gene (bottom). Figure C indicates the half-lives of $tRNA^{Val}$-ribozymes in stably ribozyme-transduced cells. The circles indicate relative amounts of $tRNA^{Val}$-ribozyme 1 (Rz1). Squares and diamonds indicate relative amounts of ribozyme 2 (Rz2) and 3 (Rz3), respectively. Bars show S.E. of results from 3 assays.

Please replace the paragraph beginning on page 16, line 4 with the following paragraph:

Figure 4 (A and B) shows the inhibition of production of the U5 LTR-luciferase fusion gene in HeLa cells. Panel A. Transient expression in HeLa cells. Both the target-expressing plasmid and pUCdt-Rz encoding a ribozyme were used to co-transfect HeLa cells. Panel B. Transient expression in stably ribozyme-transduced cells. Two independent clones were selected for each construct with similar levels of transcription of the inserted gene ($tRNA^{Val}$ or $tRNA^{Val}$-ribozyme). Only the target-expressing plasmid was used to transfect ribozyme-producing HeLa cells. Bars show S.E. of results from 5 assays.

Please replace the paragraph beginning on page 16, line 15 with the following paragraph:

Figure 5 (A and B) is a schematic representation of the HIV vector. The expression cassette for each $tRNA^{Val}$-ribozyme was inserted into the SalI site immediately upstream of TK-neo^r in HIV-I-derived vector (A) to yield a retroviral vector, HIVRibo.N, that encoded a $tRNA^{Val}$-ribozyme(B). Ψ indicates a packaging signal.

Please replace the paragraph beginning on page 16, line 21 with the following paragraph:

Figure 6 (A-C) shows quantitation of the expression of $tRNA^{Val}$-ribozyme in stably ribozyme-transduced H9 cells (CD4+ T cells) and inhibition of production of p24 in the transduced cells. Panel A. Quantitation of results, shown in B, of Southern blotting analysis of the RT-PCR-amplified ribozyme from two independent clones of ribozyme-transduced H9 cells. Products of PCR after 13, 15, and 17 cycles were analyzed by Southern blotting using a ^{32}P-labeled oligonucleotide probe. Squares and circles indicate the results with transduced cells of the ribozyme 2 (Rz2) and the ribozyme 3 (Rz3), respectively. Panel B indicates the results of Southern blotting. Panel C. Cells were cultured for 11 days after infection with HIV-1 NL432. Small aliquots of supernatant were prepared from each culture on days 3, 7, and 11. Levels of p24 antigen were determined by HIV-1 antigen-capture ELISA. The triangles indicate the result of $tRNA^{Val}$-ribozyme 1 (Rz1). Squares and circles indicate the results with the ribozyme 2 (Rz2) and ribozyme 3 (Rz3), respectively. Triangles indicate the results with the control.

Please replace the paragraph beginning on page 17, line 12 with the following paragraph:

Figure 7 (A-D) shows intracellular localization of the $tRNA^{Val}$-ribozyme. Northern blotting analysis was performed using RNA from each intracellular fraction. Nucleic and cytoplasmic RNAs were prepared separately from cells that had been stably transduced with the gene for a ribozyme (the $tRNA^{Val}$-ribozyme-producing HeLa

cells used in the experiments for which results are given in Figure 4B). A and C show the results obtained with a ^{32}P-labeled probe specific for the tRNA^{Val}-ribozyme. B and D show controls: Contamination of the cytoplasmic fractions was examined with a probe specific for the transcript of the natural U6 gene.